DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION F

CLINICAL SAFETY AND EFFICACY STUDIES

Tuesday, February 15, 2005

3:30 p.m.

Marriott Crystal Gateway
1700 Jefferson Davis Highway
Arlington, Virginia

PARTICIPANTS

MODERATORS:

DAVID ORLOFF, MD, FDA/CDER

MARC WALTON, FDA/CBER

DOROTHY SCOTT, MD, FDA/CBER

DAWN VIVEASH

YAFIT STARK, Ph.D

P R O C E E D I N G S

DR. WALTON: I think we will begin the second session. Thank you for all coming to the second breakout session on the clinical safety and efficacy studies.

I am Marc Walton, from the FDA. I have with me my co-moderators from the FDA, Dorothy Scott and David Orloff, as well as our panel members from industry, Yafit Stark and Dawn Viveash.

We will begin with a few introductory remarks from Yafit Stark and Dawn Viveash, and then we will move to putting up some questions and look forward to some vigorous discussion from people.

So to start with, we will have some remarks from Yafit Stark, who is with TEVA Pharmaceuticals.

DR. STARK: Thank you, Marc. Good afternoon. It is a pleasure to do it the second time, hoping that the second time will be much better from the first. After all, we gain some experience and we probably resolve some

uncertainties during the first session.

First of all, it is a pleasure for me to come all the way from Israel to Arlington to participate in this session, and I would like to thank the organizers and the FDA members for inviting me to this session.

Secondly, I would also like to thank the presenters in the plenary session, Dr. Siegel and Dr. Carole Ben-Maimon, for laying the ground for my presentation and Dawn's presentation.

Our major objective today is to discuss how we are going to clinically develop the biopharmaceutical generic.

Hearing now that this is not going to be a simple task, our major concern is to assure that we maintain the patient welfare, safety and efficacy.

And how shall we minimize the risks to the patients? That is the major question that we should ask ourselves.

So the first question that we need to ask, should we conduct clinical studies. So following, of course, all the process that the best

pharmaceutical companies are trying to assess the uncertainties and to assess the comparability of the biopharmaceutical generic versus the innovator, they are trying to look for the analytical, as well as the biological characterization, and if there are uncertainties that are observed either by the analytical or by the biological, maybe by the animal, then we go to pharmacokinetics and/or pharmacodynamics.

If there are still uncertainties being observed, then we will come into go to clinical studies.

In general, the situation of the biopharmaceutical generic is a little bit different from the innovator, and I a lucky to be both playing a role both in the innovator R&D, of which I have been involved with developing innovative product for the last 18 years, but, also, doing biologic generic.

The difference between the innovative and the generic company is that the innovators are starting from scratch. We have to build our level

of confidence, our experience within the product development, and the innovators, when they start their development, there is a lot of information accumulated during the development of the innovator, but, also, during the marketing phase, and they can benefit from this information.

So in general, we can rely pretty much on the extensive clinical experience that exists with the brand, as well as with the indication, and sometimes clinical studies are not warranted if we have enough clinical information, but we will discuss in our breakout session when should we conduct clinical studies.

Now, the question if clinical studies are needed, then we should ask ourselves how shall we design the clinical studies; what should be the major objective of the clinical study.

This morning we have heard in the plenary session that our clinical development should be targeted, meaning that we should focus on specific questions to answer scientifically clinically sound questions, and for that we should, of course,

design the study to answer these questions.

During the development of the innovator and sometimes during the post-marketing, surrogate markers have been utilized, sometimes they have been validated, and if they exist, it is better to use the surrogate markers as the primary outcome during the clinical study.

Recently, I have been hearing, also, that even for the innovator, there are publications that were done by MDA members to advocate the use of surrogate markers even in confirmatory clinical studies via the innovators.

In cases of which surrogate markers do not exist or are not validated, we will advocate to use, of course, the clinical outcome measure as the primary outcome.

Safety should be our major concern during the development and during the post-marketing, and, of course, the safety profile that is comparable to that of the brand can also be assured through all the process that we have described before.

We can look at characterization and we can

look at animal models and pharmacokinetics, and well as pharmacodynamics, and only by then we can, of course, design our clinical studies to answer safety concerns.

As with all marketed products, of course, safety of protein products is closely monitored, both during the development, if clinical studies are warranted, as well as during the market by adopting an active pharmacovigilance plan.

With this plan, we will be able to expose many patients, to look for subtle differences, of which clinical studies sometimes do not.

I hope that with the brief presentation, I have summarized the two presentations in the plenary session and I would like to invite my colleague, Dawn.

DR. VIVEASH: Thank you. I am also very pleased to be here. It is a very important topic for discussion today. I think the discussion should really pick up from the great presentations we had this morning.

The comments that I am going to make in my

presentation really are not novel or new. They are very similar, totally consistent with a lot of the comments that have been made earlier on.

So I will try not to go into too much detail.

One of the very reassuring things is that we have a common goal, whether it's the regulatory authorities, whether it's the innovator industry or the generics industry. We want to get safe, effective products to patients, and we have to be very careful in doing this that we don't do anything that will compromise patient safety in particular.

We all realize that given the complexity of biologics, that we can't take the identical approach that has been taken with small molecules. We can learn lessons from that, but we need to come up with a unique approach for any follow-on protein products.

The development programs we use for innovator products really are not substantially different in principle from the programs that we

should consider for follow-on products, but we can, of course, learn and will learn and utilize knowledge that has been gained from the innovator.

In the prior session, we heard a lot of discussion around the analytics, the biologic characterization, the immunogenicity, PK/PD studies, and whilst the science has come a long way and we can now give a lot of information in terms of characterizing products, there are always limitations to these techniques.

The problem with the limitations is we are left with some uncertainty and that uncertainty, as Dr. Siegel pointed out this morning, really translates into risk.

So the question for us today is how do we minimize the risk and how do we manage residual risk, because even at the time of approval of innovator products, we are not in a zero risk environment.

The complexity of the products clearly is something that will drive the answer to what clinical data is required, but I would like to

suggest that it is not just the complexity of the molecule. It is the complexity of the biology and the clinical setting, as well.

On the next slide, I have just listed some considerations regarding the clinical and biologic complexity and the issues that might lead us to consider we need clinical studies to address some of the uncertainty and to minimize the risk.

There are concerns for both efficacy and safety, even though much of the time we focus on safety. I think there were good examples given today where efficacy can be problematic.

The nature of the product in the therapeutic setting will influence the type and the level of concern and should direct the clinical approach. So I would agree totally with Yafit that the approach that we take will be focused and targeted to specific issues.

We need to take into account issues such as what is known about mechanism of action, structure-activity relationships. Do we understand what the determinants of safety are? Do we

understand the determinants of efficacy?

If we see any changes in the structural characteristics, what does that mean in the clinic? Do we understand that or is it a black box?

How well does the PK and PD, if we choose to do PD, how does that correlate with efficacy? How does it correlate with safety?

Then in terms of the antibodies, that's a subject for an entire separate session and I presume most of you went to that breakout. We need to think about the clinical consequences and we may embed that into our clinical program, and the consequences, as you know, range from no clinical consequence at all through a large account of reaction, impact on clearance through very dramatic adverse effects, for example, as were seen with PRCA.

The immune status and the general health status of the patient may impact what we see. So we need to take that into consideration, as well as the route of administration and potentially even issues related to presentation.

So at the end of the day, I would suggest, in general principle, where there is uncertainty, we can reduce the uncertainty by generating more data and clinical data may well help us on the pathway to approval.

So what factors should be considered in designing appropriate studies? I'm not going to go through the first list, because this is the standard list of issues that you think about when you are designing any clinical studies, not just for a follow-on.

You need to have a clear objective and hypothesis and then you construct the study, including end points, around those considerations.

There are some specific issues that come up with regard to follow-on products. If you are doing a head-to-head comparison, it is a comparative study and you are doing, say, a non-inferiority design. What are the acceptable margins for non-inferiority? Are there specific adverse events of interest? Can we characterize them? We need to consider what is their level of

frequency.

Specific issues also might include questions such as do we need to study all indications? Can we study just one indication? Does efficacy in one indication allow us to project efficacy in another? That might tie back to what we know about mechanism of action, structure-activity relationships, et cetera.

Is the safety in one setting predictive of another? We heard this morning that with Eprex, the safety signal was actually noted in the renal population, but not in the oncology population, and still to date has not really been established in that population.

We need to think about the latency of events, chronic versus short-term treatment, and other aspects, such as route of administration.

Then even having done, if we agree that there are situations where we need to do clinical assessment prior to approval, there may still be unknowns and those unknowns could be characterized in the post-approval setting.

I am going to pause and just give a couple of examples of where Amgen has utilized clinical studies and has made a determination that studies are necessary, even when we have made a process change. The two examples are for products that have been used quite extensively.

One is Aranesp, erythropoietin, and the other is an example with Enbrel. In both situations, we are looking at major process changes, including a change in cell line.

In the situation with Aranesp, and these are both situations that are ongoing, so I don't have full data sets, but the situation with Aranesp is such that to date, we have comparability. Using the analytical approach, we have comparability. We have bioequivalence.

But nonetheless, given the major concerns we have regarding erythropoietin safety, we felt it was appropriate, and the regulators agreed, that we should establish some clinical efficacy and safety data.

So we will be studying a substantial

number of patients to identify whether there are any surprises in terms of clinical response.

We recognize that we are unlikely to see PRCA. If we see PRCA, we've got a major issue, but most likely we won't see PRCA. However, we can look at immunogenicity. Again, that has been discussed in the other session.

The situation with Enbrel is a little different, but, again, one that may occur with a follow-on product where you characterize the product and the more you can characterize the product, I think as Jay pointed out, the more likely it is you will see differences.

Most of those differences may not have any relevance or meaning, but you may not know that.

In the case of Enbrel, we have changed the process such that we have reduced the amount of misfolded protein and, in addition, there are some very minor changes in glycosylation patterns.

Again, because of those differences, we feel that we can't, with confidence, say these are clinically--the product is clinically the same as

the current product until we have established that in the clinic.

So I think those examples are relevant to the follow-on issue.

So at the end of the day, we get through the approval process and there may be some uncertainties, and, again, depending on the specific uncertainties, depending on how robust the preapproval clinical database is, we may feel a need to do additional post-marketing work.

It may be as simple as just routine surveillance, which is commonplace and required for all products, or if there is a specific question, it may be more extensive, in which case we may look at some additional data collection methodology, such as registries.

The immunogenicity in particular I think is very unpredictable and I don't think we can reasonably extrapolate from one product to a follow-on product. So I think there is going to be a need at some stage to characterize that, and the unique characteristics should be reflected in the

unique labeling for those products.

I think the only other thing that I would like to say about the pharmacovigilance, in particular, the passive surveillance program, is it only has value if you have good data. One key data element is knowing what product the patient was exposed to, and I think this is a particular problem if we look at products being substitutable, where the health care provider may not have appropriate or correct, accurate information about which product the patient received.

So the prescriber certainly needs to be knowledgeable and we would advocate the prescriber needs to be in the decision-making step as to which product is received.

So I think with that, so we can allow a lot of time for discussion, I will hand it back to Marc. Thank you.

DR. WALTON: Thank you, Dawn. Thank you, Yafit. I think in addition to the discussions we had this morning, you have done a very good job of laying the groundwork for having a good discussion

here this afternoon.

To facilitate that, we have three specific questions, and I think for the organization of the afternoon, we will try to address each one in turn and spend some time on each one to ensure that we can get to each of them.

Also, for the structure, I want to remind people that the structure here is we are looking for people to provide their comments and advice and perspective based upon their experience and their knowledge, the degree to which you can give us a more concrete understanding of your experience that leads to your viewpoints will make the point better and help us understand how to utilize the advice, as well as the purpose of the panel here is not really to be answering the questions today.

We are really looking more to hear the advice and the experience that people in the room have.

We will start with the first question today, which is in what situations would safety and/or clinical studies be needed and why. As I

said, the more one can be concrete about the specific situations and the circumstances that would lead to making the decision one way or the other, the more useful our discussion will be.

If we have anyone who would like to address some points on this matter, please come to one of the microphones. Please state your name and your affiliation as you begin speaking.

DR. NAKTINIS: I am Vytautas Naktinis. I am a consultant, working for TEVA right now.

My question is precipitated directly by the presentation, short presentation by Dr. Viveash. Two examples, excellent examples were given. When a company decided to move to clinical trials after making process changes and seeing differences, what this story tells to us is that analytical tools are available within the company which allow to detect differences and many, discussions around this meeting and the previous meeting, this particular statement was very much challenged, and saying, oh, no, no, analytics cannot tell you anything, and you have to do

clinical trials.

I would ask would you go for clinical trials if changes you observed would be significantly less or not detected? That is perhaps a question.

DR. WALTON: Before you step away, perhaps you could provide a definition of what you regard as significant changes or non-significant changes.

DR. NAKTINIS: In fact, I would like this question to be answered by the innovator. To me, it's a clear answer what I would do as a follow-on manufacturer.

Of course, you have variations of certain parameters. Let's take one parameter, not to complicate the issue.

If a manufacturing change is within a variation or perhaps below, if, let's say, dimer or something, perhaps you would not go for clinical trial to evaluate whether it is still okay.

So, clearly, something else happened. Either your product now moved above specification or something new appeared in your profile. That is

a case which would trigger a clinical trial. That is my understanding.

DR. VIVEASH: I will try to address that. I gave two different examples, and deliberately gave different examples because I think they illustrate two different--well, same approach, but in two different settings.

The first example with Aranesp is one where as we have the analytical information, and, obviously, we can characterize the product extremely well, and we don't see any differences, but because of our concerns with erythropoietins in general and, in particular, given the situation that has arisen with immunogenicity, we're going to do clinical studies regardless, and that is, in part, driven because we have made such a major change in the process.

On the other hand, the other example with Enbrel, we have observed some changes and when we observe changes, we always look at that in the context of what is our experience, what have we seen previously in the manufacturing, taking into

account the entire manufacturing history, oftentimes taking into account what has actually been in the clinic, and then taking into account what difference might this make.

So for example, with the misfolded protein, our belief and the data would suggest misfolded protein is not active, and, therefore, having less could actually add greater pharmacologic activity.

We don't project that that will have any negative impact, but we feel we need to assess it.

Then if you take another example, which will be hypothetical, because I'm not calling up a real live example, but we often make small, discreet changes to the process, where we are able to look and if we see very minor changes that are within the scope of what we have seen previously, then we often typically would not do clinical studies.

So I think it is very situational. It depends on the magnitude of the change in the manufacturing process. If it is a big change, our

threshold for doing clinical studies is low and what we understand about the clinical consequences.

So you need to integrate both.

DR. PETTER: Ram Petter, TEVA.

DR. ORLOFF: Can I just follow-up with a question for everybody? Once these judgments are made that there is sufficient uncertainty based upon structural characterization and everything short of clinical studies, should the--this kind of merges or melds into the second question, should the studies necessarily be designed then as comparator studies, comparative safety and efficacy studies?

And a follow-up to that is to what extent, in these specific examples, where--while it seems at least from the way you tell the story that the intent was there to make sure nothing was missed, to what extent are those studies designed and powered to exclude some significant inferior efficacy or safety, to use Dr. Siegel's phrases from this morning?

DR. WALTON: Actually, I think those are

the second question. I think before we miss our chance to work on the first question. Was there somebody else that had a comment?

DR. NAKTINIS: I think it was a great answer for us for follow-on manufacturers which came from Dr. Viveash. Exactly. If we see changes which are significant, and we judge significance based on our knowledge about a particular product, which, again, follow-on manufacturer accumulates to the same degree as innovator, so we make intelligent judgment do we need to push development into clinical trials.

If insignificant, we can limit our program. To what limit, I better stay away.

DR. WALTON: Before you walk away, let me ask you another question, following on to your answer.

If the judgment is going to be made based upon that particular manufacturer's experience, that manufacturer, that follow-on manufacturer may well have experience with a variety of different protein products, but would not, of course, have

the same extensive experience with that particular follow-on as the innovator.

So to what degree do you think that the innovator's specific experience with that specific protein is important versus more general experience with follow-on proteins and judging the significance of differences that are discerned?

DR. NAKTINIS: We are moving back to the session A of yesterday. I'll make the principle points first.

Follow-on manufacturer develops products, protein products in a full capacity of CMC section, exactly what the innovator does. It is lengthy, many years process, which includes development assays, validated assays, knowing the protein, knowing structure.

So, of course, a generic manufacturer doesn't start to develop a follow-on protein in a vacuum in the absence of knowledge, what has been done from that source of information could be available, and, of course, based on the previous knowledge on other proteins, which you mentioned,

as well.

That is very much strong supportive knowledge which helps the follow-on manufacturer to design specification, to think what specific factors should be looked at, and so on and so on.

That's the basic picture.

DR. WALTON: Thank you.

DR. PETTER: Ram Petter, TEVA Pharmaceuticals. Just to add another aspect to the description of the process and how thorough is the development in the biogeneric industry.

I would just like to stress that Sicor Biotech, a TEVA subsidiary, in manufacturing and selling interferon alpha 2B in the last 15 years, over nine million doses were sold.

So I think there is no doubt that we are pretty much familiar with the process. We know the process as good as the innovator, and, therefore, we are capable to interpret any change or any modification we may observe.

DR. SIEGEL: I have no doubt that there are companies all over the world in the generic

industry that can make quality products, but to say that the CMC is the same, I think what troubles me most is that I would imagine that biogenerics are not acquiring the cell line from the innovator company.

So they are using a different cell line and experience has taught that changing the cell line is perhaps the most, certainly one of the most profound changes you can make in manufacturing.

Now, if you have a belief that everything that that could possibly change you can detect in assays and then you know what its implications are going to be, then I suppose that could lead to the conclusion that you don't need to do clinical studies.

I think when you change a cell line, whether you are an innovator or a manufacturer of a generic, if you introduce that material into patients without doing clinical studies, you are putting patients at risk and you are putting your product at risk.

So my answer to this question is what is

the threshold; well, if you are using a different cell line, that triggers it right there.

DR. COHEN: Hillel Cohen, Novartis Pharmaceuticals. Two comments along the lines of what Dr. Siegel made.

When you are choosing a new process, a follow-on, by definition, is going to be introducing a new process. It might be based on published literature, but certainly the equipment is going to be different, the assays, certainly there will be many differences.

As mentioned, there will be a new cell line or a different cell line. These are changes which the FDA and European regulators have already deemed in the categories as being a major change that triggers a clinical study.

That answers the very first question, under which conditions would they be required. That answers it really right then and there.

Now the question is what type of clinical study. I think certainly, from my perspective, I think what you need to do is you need to confirm

the clinical efficacy. We no longer need to prove that EPO will save lives from a cardiovascular perspective, that growth hormone makes children grow.

These are facts that have already been established, but you have to establish in comparative clinical studies that your follow-on product will elicit a response similar to that of the innovator. That is point one.

The other point I would like to make is that there is still value at looking at the experience of the innovator. Have we learned anything specific? Are there specific adverse events? Are there specific pharmacokinetic parameters that are now known that may not have been known when the innovator was first approved.

If there are specific concerns, that may be, and I emphasize may be, because it is still case-by-case basis, there may be another area in which a focused clinical trial would be appropriate, I guess, for both efficacy or safety.

DR. WALTON: Thank you.

DR. NAVEH: David Naveh, Bayer. I think that the phase one PK study captures not only the molecule, but, also, formulation, device, hypersensitivities, and tolerability, which you can't always capture in animal studies.

So I can't envision a situation where you would not do a PK study, a very limited study, before you start selling the drug.

In my own opinion, the other risk is immunogenicity of the product. I won't get into whether it should be head-to-head. I don't think it should be head-to-head, because original developers don't really have that as a self-standing trial.

When we develop drugs, during our efficacy trials, one of the end points we have is usually a safety end point that speaks to the issue of antibody formation.

So we have heard extremes here. Some people say that you need to show efficacy in a comparative trial. Thousands of patients, I think that is, in my own opinion, unwarranted, because

you know the molecule, you know the indication.

I think that there is no such thing as identical and beyond the comments about cell line, I don't think that if you would do a follow-on, you would actually have identical formulation device, injection, injection device, et cetera.

So a PK study covers that. Then the second issue is, in my opinion, immunogenicity, and, again, if a 100 individuals get a protein and ten of them, for example, elicit antibodies to the protein, to the original protein, within two or three months, the 90 that remain on the drug and do not exhibit antibodies, except for spontaneous formation of antibodies, are the ones that should be checked to see if they would now elicit antibodies against the new drug.

If drug does have new epitopes, I think that based on experience with several proteins that I have dealt with, you would see it in a majority of patients after limited exposure days.

So you're not talking about a large number of patients. You are looking at gross

antigenicity.

That's from my own experience.

DR. WALTON: You said that this was based on several protein products that you had worked on. Can you give us a sense of which ones?

DR. NAVEH: I'll be happy to. I can share one that is well known and published. Hemophilia I think is a very good case study for studying antigenicity. It is a case where, when you get antibodies, you really have clinical effects, because you can't treat a bleeding patient with another Factor 8.

There have been two cases of changes in manufacturing which resulted in new antigenicity and in both cases, by the way, you could also see this analytically, but only retrospectively.

So analytic characterization cannot predict, and, in both cases, within, I would say, from memory, within 15 to 20 days of exposure, antibodies developed. They were transient. They disappeared after about two or three months, and they developed in the majority of individuals that

got the, I will call it, defective or changed drug.

As other people said, I don't think you should try to capture the three out of a 1,000 events which are innate to the original molecule.

That is the risk that will be part of the pharmacovigilance that is needed in the new drug.

And your comment, it is very clear that there are concrete, in which there are very advanced protein producers, but I venture to say that the pharmacovigilance in them is not as tight as in the U.S., but it does speak to the fact that other people can make drugs and they work, protein drugs.

DR. WALTON: Thank you.

FROM THE AUDIENCE: Just a quick comment about the previous statement about testing immunogenicity in subjects who didn't develop antibody with the innovator product.

Say you have a product that has three times the incidence of immunogenicity in patients naive to the drug. Don't you want to know that?

DR. WALTON: You have to speak into the

microphone so that what you are saying is captured. Please come back to the microphone and use the microphone.

DR. NAVEH: I'm not an immunologist or an MD. I'm an engineer, so I look at it maybe in a way that is a bit different.

I would say, to answer your question, what you are trying to surgically get at are the new--is the new antigenicity due to the new product and not the inherent antibody development of an individual that gets a protein, because some proteins that are made are antigenic in their nature.

So what I was proposing as a path forward was that if you would take a cohort of patients who have been on the original innovator drug for a while and, say, of a 100 patients, if I repeat the example, ten develop antibodies and, therefore, are not responders or are of the drug.

The 90 that are on the drug, the innovator's drug, are the ones that should be tested, PTP, if you will, in clinical terms, should be tested for the new drug.

It's not that simple and black and white, but I don't have the time to go into details, and then you have to forge the friendship between the rate of development or seroconversion in the new drug to what the baseline seroconversion is, spontaneous seroconversion is in the original drug.

But you're looking at the incremental new antigenicity of the new product and not the overall antigenicity of the product to naive patients.

And if you would want that in your package insert, you would have to do a trial later on, the innovators, to show that there is no difference with naive patients, but that could be possibly part of a phase four trial.

FROM THE AUDIENCE: I understand, but I still think it could be a stochastic process, right? In other words, you could develop the antibody three times as much. It doesn't matter whether you develop with the original product or not.

But anyway, I had another question I wanted to bring up. We have talked about different

levels of complexity of protein. So far, I haven't heard much distinction between what would we do based on protein complexity.

So I guess for this question about whether clinical trials are necessary and what clinical trials are necessary, what about a simple example of a protein which is small enough to be characterized by NMR, which has no glycosylation, and which might have a series of deamidations or oxidations, but a total of, say, ten or twelve known variants that are characterizable?

I know the argument will be made you can pick them all up, we're using the same techniques; but if you're talking about that level of complexity, talking about a product which has no known adverse events from the innovator trials, at least nothing that sticks out from those numbers, and at some level of immunogenicity not associated with an adverse event, I'm kind of curious to hear from the audience what they think would or would not be necessary for that type of protein, assuming that, in terms of similarity, really you saw almost

all the same variants with the innovator as with the follow-on product.

There was, obviously, some subtle differences, but not that great in terms of whatever comparator you used, whether you acquired drug substance or whether you managed to provide drug substance from drug product in some way that was shown not to bias your material.

DR. GREEN: Jim Green, Biogen Idec. Maybe I could take a crack at that within the context of my response.

DR. WALTON: Please do.

DR. GREEN: First, I think the way I would like to think about the complexity issues, the debate here started between small molecules and biologics and what do we do between both.

We have trouble with structure-function relationships and structure-activity relationships with small molecules today. Maybe within one chemical class we can predict toxicities, but across classes, still very difficult.

The complexities I think that we have

heard described today for low, moderate and high, they are all complex. They are huge proteins.

So our ability to predict structure and function at that magnitude I think is problematic.

Now, to the extent, with what kind of clinical studies would be necessary and when, I would maintain, I can't imagine a situation for a chronic use drug where there would be no requirement for clinical study, and the reason I say this, then I would put the challenge to you, is that you can't make that determination essentially in isolation.

You have to look at the data that has gone before it. Now, we have already agreed and the biogeneric folks have acknowledged that a complete CMC profile essentially would be required, state-of-the-art assessments, et cetera.

They are starting with a new cell line, new process; by definition, a major change. So the only way that they can essentially, in my view, diminish the amount of data that might be required is on the basis of some head-to-head comparison

across the spectrum of levels of assessment that we employ as part of our comparability assessments.

The biochemical assessment to confirm structure, the bioactivity assessment to confirm mechanism of action, the kinetic assessment to confirm dosimetry, the toxicologic assessment to confirm therapeutic ratio.

If all of those assessments, in your view, standing back looking at all that data, and it's not going to be identical, but you may conclude that it is similar, in that circumstance, I think you can then begin to entertain abbreviated clinical programs.

It's not no clinical program, because you may still find out, when you take that molecule into the clinic, that the dosimetry has changed, and there are examples that the FDA is aware of where that has happened, where we have concluded comparability on the basis of laboratory assessments and animal assessments, only to be misled and find it in the clinic.

So I can't imagine any situation where

there would not be clinical studies, and the scope of those clinical studies, I think you can begin to make an argument about an abbreviated program when all of the other technical assessments lead you to the conclusion that this molecule looks similar.

DR. WALTON: Thank you. I think that in the interest of time, I do want to move us more explicitly into what has just been touched upon; that is, the second question about how do we go about thinking about designing the clinical studies when they are appropriate and what would be appropriate objectives for that.

FROM THE AUDIENCE: I actually brought up the same points about this yesterday, but I have to make a disclaimer. I am not a clinician, and, also, I am not a statistician. So my view is actually from an engineer's standpoint of view of how the CMC development was done.

First is I challenge the claim made by the follow-on companies about their CMC sessions would be quite the same as the initiator's CMC session, and this is related to the design of the clinical

trial.

The reason I say so is I have worked for three companies so far, they are all innovator companies, and so I have seen at least ten approved products, the CMC part, and for all of these at least ten BLAs I have seen, they all have a section called development history.

In that section, basically, what everybody does is list all the materials they have ever made that went into the clinical trials.

So in that development history, you have different scales and literally you have processes that are slightly different from phase one, two, phase three.

So in my view, my understanding is when FDA approves a drug, you approve its safety and efficacy based upon the spectrum of the studies you have done across the whole development cycle, which included materials generated from small-scale to commercial scale.

Also, my question. Another concern is when you approve a process, we all know you have to

do three consistent runs, which is supposed to be a to-be-marketed process. But the purpose of the consistent run is to demonstrate that you can make the same product over and over, and, therefore, you are not really using your consistence run to justify your spec and your justification of the range of your spec actually comes from your development history.

If the data that you have were generated by using different scales and different types of materials that you have generated over maybe ten years of time, and they have some variations of the critical process attributes.

So in my view, I have a hard time trying to understand, for the follow-on companies, how do you do your CMC section to cover that range of the spec that you are trying to claim? Are you going to make consistent runs non-consistent to cover your range?

So then my last point is I have heard, for the follow-on companies, that the way to generate the reference standard, one way is to get the

material from the originator, then reformulate it.

I also have a concern about how do you do that. The reason is look at the innovator companies. Every time we have a manufacturing instance that we have to reformulate something or refilter something, we call that rework, reprocessing, and before we can put that product out to market, literally, you have to do a post-approval supplement to show to FDA that the material you generated by using the reprocessing is the same and it is also safe and the same efficacious as the non-reprocessed.

So I'm wondering, in this case, how the follow-on companies would demonstrate that the reference material they made by reprocessing the originator's process is actually the same.

So that is my view of what should go into the consideration of if you need to do a clinical trial for the follow-on products.

Thank you.

DR. WALTON: Thank you.

DR. NAKTINIS: Vytautas Naktinis, again,

TEVA. It is a simple answer. Just for fun, of course, come and visit one follow-on company and see how do they develop their process.

Now, to go on a serious note. I repeat, again, we develop the CMC section exactly in the way how it is described either in documents of ICH. So we start from lab scale and move through. We start at toxicology. We do stability. We do formulation development. We move upscale, whatever scale we decided to do. We do PK, sometimes PD.

Then what we ask, all the story today is can this clinical trial--if our analytical--I mean, phase three trials. If our analytical shows okay, if our CMC is okay, that is the same situation.

This is actually the second time I hear in this audience, again, questions about how do you guys make follow-on proteins and the assumption usually is that we go to some university lab, pick up strain from its bench, put that into the vessel, cook a little bit, collect something from there, put into vials, and come to FDA asking, okay, would you please, ladies and gentlemen, approve this

thing for human use.

This is totally not the story. I am sorry.

DR. DILIBERTI: Charlie DiLiberti, Barr Labs. When a brand product manufacturer makes a significant process change or a site transfer or some other change that necessitates a clinical study, and I think you gave some very good examples with Aranesp and Enbrel, I think the question is what sort of clinical studies do the brand companies do to justify that process change, and I think that can shed some light in answering this question.

I have some particular sub-questions here. In the case of drugs that have multiple indications, for example, Enbrel, which has five major indications, does your clinical study test all five of those indications or are you using a surrogate marker? What is the design? Is it a head-to-head pre-change/post-change? What are the criteria? Is it non-inferiority? Is it equivalence? Is it power to detect the rare safety

events that can happen with Enbrel? For example, sepsis, demyelinating disorders, aplastic anemia, which are very rare events, and are those tested on an equivalence or a non-inferiority basis?

DR. VIVEASH: If you would like me to address that, I can.

DR. WALTON: If you would like.

DR. VIVEASH: I'll keep it reasonably brief. I'm going to keep it reasonably high level, because much of this is proprietary information in a project that is ongoing.

The simple answer is the studies are designed to fit the question and to fit the objective and hypothesis.

So for example, if there is a question regarding efficacy, then we would typically, if we are trying to make the case that this is still Enbrel, then we do an appropriate head-to-head study, typically non-inferiority.

Depending on the situation, we may or may not study more than one indication, and a lot of that depends on the degree to which one can

extrapolate from the existing indication.

The question do we pare for rare events, no, we don't. We don't in the de novo, the initial approval studies, and we wouldn't do that in the studies to look at the manufacturing change.

We would pare it for the more common events and infections, the ones that would typically be picked up with any of our moderately sized studies, but the rare events will only come out post-marketing, and, hence, we have a very strong commitment, once we do get the product back on the marketplace per the revised process, we make every effort to try and track events according to which product was administered, was it the product before the change or after the change.

These studies, just to give you a sense, we're not talking small studies. We're not talking the full array of studies one might do for an initial approval, but we are talking a few hundred patients oftentimes. So they are quite substantial studies, very focused end points, maybe kind of more along the lines of large simplified studies,

if we can do that, focused end points, know the questions, design the study appropriately.

DR. STARK: May I ask you a question? Is it a good example for all the biopharmaceutical products that we have intention to develop? My understanding is that your product is a complex glycoprotein, that this is not a simple molecule, right?

DR. VIVEASH: I'm giving real life examples. So I think it is up to others to help understand whether that can be extrapolated to every situation.

I think there are valid questions about what about protein products that are less complex. I don't have firsthand experience with those, so I am going to shy away from answering those questions, but we were asked to provide some real life examples and that is what I have done.

So extrapolate as you wish.

FROM THE AUDIENCE: Can I just make a clarification? I don't doubt the capability of the follow-on companies to develop process, and,

actually, I am sure you start from small scale, because if anybody tells me they can have a cell line and immediately jump into the commercial scale, I will be very impressed.

The point I am trying to make is that for the originator companies, it is every type of scale and every type of small variation. Also, they all went to humans. And for you, it's not like you put small scale material and with different variations of the critical product attributes into the humans.

Another way of saying it is if you argue for no clinical trial, that means, basically, none of your material has been tested, while, for the originator--tested in humans, right? Because if you are arguing for no clinical trial, it--but if it is--but for the originator, the material went into humans, to establish the safety actually comes from different scales, comes from slightly different processes.

So they have a huge safety database to know their process space, which is, I understand, a big part of that iceberg we are talking about. So

that is my real point.

DR. MARSHALL: Mike Marshall, Novo Nordisk. I would like to add a sort of case study for an innovator making a major process change. I think I can elucidate a little bit.

We have just developed a second generation manufacturing process for insulin and insulin spot, new expression construct, meaning a new master cell bank, a new factory, and a new purification process.

We, as in our comparability program, included quality comparability, of course, and this was supplemented with PK/PD studies and immunogenicity study, which started off as an immunogenicity study, but which evolved into more general safety and some efficacy parameters were included, but basically an immunogenicity study.

Now, the requirement of the immunogenicity study was really from the authorities. We actually went to the authorities claiming that we could use the principle of comparability using the quality data alone to justify the safety and efficacy.

However, the authorities were rather uncomfortable with this, as it was a very, very major change, and we heard expressions such as it doesn't matter how sensitive your analytical methods are, you cannot exclude the possibility that you have missed an impurity, and the risk of immunogenicity is low, but cannot be ruled out.

So we arrived at a comparability program that was quality, PK/PD, and an immunogenicity study.

My point is that for a follow-on biologic coming in, also, with a new, different master cell bank, I fail to see that the requirements would be less than that that we have experienced as the innovator, remembering, also, that insulin is a small protein, is well characterized, and not a complex protein.

MR. DUCHARME: Murray Ducharme, MDS Pharma Services and University of Montreal.

I think it is hard to really talk about those issues separately. It is very difficult to talk about clinical studies without, for example,

talking about PK/PD studies, and it really depends, the study that you are going to have to do in the clinic to show equivalence of efficacy, for example, is--you are going to have to do that if you didn't do a PK/PD study that would demonstrate that in the first place.

So for example, if you are able to demonstrate very rigorously that the PK/PD is the same between two products, understanding that you have all the background characterization, blah, blah, blah, that we talked about after, and immunogenicity, then why would you need to prove that the efficacy is the same in the clinic, because you have already proven that in the PK/PD study.

Now, we know there are some instances where you cannot and you will not be able to do the PK/PD studies, and then it is very important to show that in a well designed clinical study that you have the same efficacy.

DR. WALTON: Thank you.

DR. DILIBERTI: Charlie DiLiberti, Barr

Labs. We have heard a lot today and yesterday about the vast stores of knowledge that brand companies have regarding their process space and the clinical data and preclinical data that they have on product made within the process.

Now, the question is when a brand company makes a process change, they are, by definition, stepping outside the boundaries of their known process space, and, therefore, that renders their existing store of clinical knowledge essentially irrelevant.

So I think that that should impact on the requirements for the "follow-on" situation in that we're in the same boat and we have seen and we have heard time and time again the statement made that small process changes can yield subtle changes in the product that can have completely unexpected clinical consequences.

So I don't see that the follow-on manufacturer, in the context of getting their product approved, and a brand product manufacturer, in the context of making a process change, has any

different situation.

DR. VIVEASH: Can I ask you a question regarding that? I'm not sure that I actually agree with your statement, but if you do truly believe that the clinical data is, therefore, irrelevant, if you step outside the bounds of the process, are you then advocating that we should always do clinical studies for any process change and, therefore, for any follow-on biologic, there should always be clinical study?

DR. DILIBERTI: No, I don't, because I believe that the types of changes that can result in clinically significant consequences can and, in fact, are detected analytically if the right tools are used.

FROM THE AUDIENCE: I have a little bit of answer to that question. In my view, that also goes back to the development history.

When we make process changes, if it is out of the boundary of the approved process, we have to go back to look at the history to see whether that kind of product quality attributes within that

range, whether that has ever been tested in the phase one, two, three, or animal studies.

If we have data from the previous development showing that that was okay, that is actually our justification to say why we don't need that much clinical trial.

Usually, if you have never tested and if it is totally out of the boundary, usually, people just don't make the change and a lot of times, I have to say it is not all the information that are available to public, because many of them are proprietary.

So I don't think we can generalize just by the data you can see in the public domain.

So, again, that is why I say the development history actually plays a big role in why an innovator company can do process changes and can do comparability, and that is a different case with a follow-on product, because they don't have access to that development history.

DR. DILIBERTI: Charlie DiLiberti, Barr Labs. The previous statement implicitly assumes

that the analytical and other comparative tools that lead up to the clinical studies are, in fact, sensitive to detecting changes that could be clinically significant.

DR. WALTON: Thank you. In the interest of time, I would like to move on to our third question or topic for discussion this afternoon, which is to talk about which concerns can be addressed in the post-marketing surveillance as part of our safety assessment of follow-on products, and which things cannot be assessed, and a part of this is addressing the issue, as has been mentioned this afternoon, as well as this morning, about the tracking of exactly which product a patient has received when they have an adverse event that is reported and the difficulty that this may or may not pose in our interpreting that data.

So I would like to hear some comments and viewpoints regarding the post-marketing.

MR. DUCHARME: Murray Ducharme, MDS Pharma Services, University of Montreal. Actually, I don't understand the question, because we are in

this session about efficacy and toxicity. Is the question saying that we would address efficacy and safety after post-marketing?

For me, this question is more related to immunogenicity, in my mind, which was in another session.

DR. WALTON: That might actually be an answer, that is, to the question. I don't think that in post-marketing surveillance, we are talking about the ability to really assess efficacy, but we are talking about the ability to learn something about safety.

A question that is out there is can we learn important things that we need to about safety outside of immunogenicity in post-marketing surveillance or is post-marketing surveillance so ill suited to that that any questions we have must be answered pre-marketing.

DR. DILIBERTI: Charlie DiLiberti, Barr Labs. I think it was stated earlier that one useful application of post-marketing surveillance is in precisely those rare safety events that occur

so infrequently that it is difficult to detect them reliably in clinical studies.

DR. WALTON: Can you comment on the topic of the tracking ability; that is, knowing exactly which product the patient has received and to what degree you think this does or does not pose a problem?

DR. DILIBERTI: I personally don't see how it would pose a problem, because, quite frankly, when we get adverse event reports, we know it is our product and not some other product.

DR. SCOTT: Let me just comment on that, having looked at a lot of adverse event reports, in particular, for immune globulin, that the FDA receives from manufacturers and from outside pharmacists, as a rule.

If I had to guess, I would say at least ten percent of those do not have the name of the product listed and many of them do not have a lot number, which you could at least trace a lot number even back to a name.

I think it is critically important for

adverse events, potential adverse events, such as viral transmissions and so forth, to have that information. It is not, if you will, required or it is just simply not done, and that would seem quite important.

DR. DI DILIBERTI: Well, we already have essentially a multisource situation for a number of protein products. We have it for the insulins, we have it for human growth hormone and a number of other products, and, presumably, that hasn't been a problem historically.

DR. SCOTT: I think you need to look at the data to find that out, because you only need to have one problem where you aren't able to trace that product or find the manufacturing problem that led to that adverse event, if there was one.

DR. DI DILIBERTI: Does that mean we need to do something about withdrawing some of the currently approved products from the market, where they are multisource?

DR. SCOTT: No, no, no. What I am saying is that if you don't have the data, you don't know

what happened, and if you don't know what happened, you can't look at the manufacturing or any other problem that might be related to that adverse event, if it is related.

DR. VIVEASH: Maybe I could just elaborate, because I did have a point in my presentation on the importance of identifying the product.

I think quite often spontaneous events, when they first come in, are actually lacking significant information.

The concern I was really getting to is if a prescriber prescribed the brand product and, unbeknownst to them, it was substituted at the pharmacy level with a follow-on product, then when they report it, they will report it to the innovator and there may never be a question raised about whether it was a different product, and that will just confuse the whole picture.

Had that occurred, say, the PRCA situation, had that arisen in a generic or a follow-on protein product environment, we may never

have understood that it was related to one product and a specific process change that was made. It would have probably been more attributed to the class.

So I think that is the issue that I was really driving at there.

DR. COHEN: Hillel Cohen, Novartis Pharmaceuticals. Maybe Dawn just directly answered your question. First, for a follow-on product, where you may or may not have a separate brand name, depending on the marketing interest of the company, probably the best way to track it might be through the NDC codes, in which case you may actually have to go back to the pharmacy that prescribed the product in this particular situation.

That is not necessarily the case for an innovator product, but for follow-ons, I would imagine that would be an important parameter to help track it down.

I share your concern that adverse event reports almost invariably require follow-up on the

part of the company, and I wouldn't be surprised if a report came into one company and it was related to another. That is a real possibility.

At present, in the U.S., I think the NDC codes would probably be the best way to go.

Now, a few other comments, please. It is important, when the follow-on product is approved, it will have a label that is near identical, within parameters, I would imagine, to that of the innovator.

However, post-marketing safety surveillance is really critical to establish whether the long-term safety profile is the same or is not the same.

Clearly, over time, being that there is separate reporting for both products, there will be a divergence in the percentage of adverse events reported for a given product. It is inevitable.

It is inevitable that the labels will begin to diverge in that particular parameter.

Now, there are two aspects of post-marketing surveillance and I agree with

comments previously that generics and branded pharmaceuticals both have the same standards.

You have the spontaneous reports, which are on a case-by-case basis and are investigated individually. You may need expedited reporting if it's not in the label.

You may need targeted reporting of specific adverse events if it is known to be a problem with the class.

But the other important parameter is the periodic accumulation, every six months or so, with the PSUR, and then that serves as the basis at which you have to evaluate and understand whether a pattern is emerging.

In this respect, I think the follow-ons and the branded should have the same requirements. I think we would, again, learn from the innovator product, if there is a particular adverse event that is known about, a particular problem, but the benefit-risk is still sufficiently high that we want to market this particular product, that is fine, but you may want to have a targeted reporting

mechanism for that particular event.

So I think there are lessons to be learned from the innovator that can be applied for the generic, but I think, in general, you should have a level playing field across the board.

DR. WALTON: Thank you. Do we have any other comments regarding post-marketing reporting and the ability of--yes.

MR. DUCHARME: Murray Ducharme, MDS Pharma Services, University of Montreal. I am just basically in agreement with some of the comments that I have heard before.

My mother worked for 20 years at Health Canada in the adverse events division and she was telling me all the time that when she was getting adverse events, it was always on the active drug, never on the trade name, and she would call back and try to find which was the manufacturer and she would never be able to find it.

I can tell you that, as a pharmacist, when I work in the clinic, in the United States and in Canada, actually, when we had adverse events, we

were always concerned with the active ingredient.

We were not looking at the trade name. So it's a big problem.

Proteins, in a way, if you only have one protein on the market, then it solves the issue. But if you have a different one in the hospital and if you have different--that are not switchable and physicians and pharmacists still will be concerned with GCSF or they may not know which brand name was administered.

So it will still be a similar problem.

DR. DI DILIBERTI: Charlie DiLiberti, Barr Labs. The problem is not, I think, unique to protein products. A similar concern could potentially exist for small molecule products which can be multisource and genericized, particularly in the case of narrow therapeutic index drugs, where a very small change in the amount of drug delivered can have a major change on the safety profile.

It is really a question of what systems do we have in place across the board for both small molecules and protein products to capture adverse

event reporting. I don't think it is unique to proteins.

DR. WALTON: Any other discussion relating to the post-marketing reporting? Do we have any other topics or questions or viewpoints that anyone in attendance here would like to bring up?

DR. SCOTT: Just with regard to post-marketing surveillance. In the last session, there was a discussion concerning when a registry or some form of active surveillance might be needed, and I wondered if the audience has any comments on that.

What would be the threshold?

DR. COHEN: Hillel Cohen, Novartis Pharmaceuticals. To directly answer the question about registries, I have actually been involved with other products that have had registries, and I think a situation exists, as I mentioned before, if the innovator product has a registry, Accutane, as an example, is something that we would expect, as consumers of these products, to be following along with the follow-on products.

I don't see a reason why you would expect the follow-on to have a different reason for which a registry would be needed if it wasn't present for the innovator.

DR. WALTON: Okay.

DR. DI DILIBERTI: Charlie DiLiberti, Barr Labs. Just to address that final point. In the small molecule world, when generic drugs are approved, where the brand product does have a registry, we do, in fact, have our own registries to mimic the registries of the brand.

We already do that. My company already markets a generic equivalent to isotretinoin or Accutane, and we have our own registry for that.

DR. WALTON: Thank you.

MR. TANTILLA: Just on that point, to clarify what Charlie said. Nick Tantilla, Barr Labs.

In fact, in some instances, the generic company will share the same registry that is used by the brand name company. In fact, isotretinoin is one example where going forward, there will be a

combined registry with four manufacturers, three generics and one brand, that will be sharing the same and there are other opportunities that we will see in the future, going forward, where brands and generics may, in fact, share the same pregnancy registry or other registry.

DR. KOZLOWSKI: Steve Kozlowski, FDA. Just a follow-up on the question I asked about less complex. Again, these are very complex molecules, in any case.

But there was a comment made about a change in insulin requiring immunogenicity and PK/PD studies and other studies.

So what I was curious about is what the numbers of patients were required for those changes and how they would compare to licensing a new product.

FROM THE AUDIENCE: The patient numbers in the immunogenicity study were about a 113. So it's divided up into two groups, a comparative study, and the PK/PD was 25 healthy volunteers.

DR. KOZLOWSKI: And would you comment on

what would be required if you were filing a new 505(b)(1) for insulin?

FROM THE AUDIENCE: I don't know what that would be. I would imagine more so.

DR. KOZLOWSKI: I'm curious. How different are those numbers?

FROM THE AUDIENCE: They don't necessarily--there is no specific number. I mean, I think what, Steve, you have gotten to is something that, unfortunately, I don't know that we got into much detail in this discussion, but there is a question of level of suspicion and of the specifics of the suspicion of risk or of inferior efficacy that have got to direct and render a rational program going forward.

For an innovator insulin, so much is known about insulin. If it is native sequence, you don't have to establish that insulin lowers glucose, that insulin itself lowers glucose. You know that. You don't have to establish that insulin is a treatment for diabetes. We already know that.

What you have to establish is that your

insulin is pure, active, and non-immunogenic, and that doesn't necessarily require thousands of patients.

On the other hand, for a more complex product, as I think you and others have alluded to, for more complex products or where the level of uncertainty and, therefore, the level of concern, the level of uncertainty is greater and the level of concern is, therefore, greater, more extensive investigations may be necessary.

Again, I mean, going back--I see Jay Siegel behind you, but he asked three fundamental questions in his talk this morning, which I think really, my opinion is that we do need to keep these in mind, and he said, if I might quote, "How much risk of inferior clinical safety and efficacy is acceptable? What is the nature of the residual risk of clinical inferiority? And then once you have made those decisions, how do they get addressed?"

In some cases, the risk is high, the nature of the risk is severe, and you need a full program to exclude the risk or at least to define

it. In other cases, the risk is low. It might be clinically monitorable. The nature of the risk might be one that is, patient by patient, not a catastrophic potentiality, in which case you can address it with less intensive efforts.

DR. SIEGEL: I want to come back to the question of registries and a comment that was made just a little bit ago, that a speaker said no reason for registries if the innovator has none, I think a reasonable comment, I think, under certain assumptions, and I want to make sure we are clear about those assumptions.

So the main reason there are registries and, indeed, the main reasons for post-marketing surveillance are to look at rare events, sometimes to look at chronic events, sometimes, in the case of post-marketing surveillance more than registries, to look at emerging events that may be seen in settings of clinical use, off-label use, concomitant combinations, ill patients, people that might not have been studied with concomitant

illness, that may not have been studied in the clinical trials, where you may see emerging adverse events.

One of the things that hasn't been discussed here, and so I'm guessing that nobody supports it, but I wonder if that is right, but has been discussed elsewhere, is the potential to use post-marketing surveillance to address other safety issues that could be addressed other ways pre-marketing, but as a way, just as a backup, even for more common things that could be studied.

I assume then there is a broad consensus that safety issues that can be addressed pre-marketing should be addressed pre-marketing. Is that fair to state?

DR. ORLOFF: This question actually came up at the last session of this. We didn't have an answer to it either.

The question is can you essentially save on your pre-marketing investigations, relying on the power of post-marketing surveillance, if you will, and I don't think we had an answer to it.

But before you go, on the question of registries, I mean, most of the time, to my recollection, registries, per se, are at least initially directed at keeping an eye on either things you know about or specific things you suspect.

In other words, they are not intended to find things that you had no idea existed, because even in registries, a registry, per se, is not set up as a formal epidemiologic case control type study, where you can necessarily infer causality.

If you believe that a aplastic anemia is a risk of erythropoietin products that might be contaminated or have adjuvant activity in them, then you are looking for that and there is an assumption, when a patient getting erythropoietin, gets aplastic anemia or pure red cell aplasia, that it was caused by drug.

There is a background rate, but you are not really all that concerned with it, because it is so rare, I guess.

Anyway, so this does not--the concept of

registry, because one of the--the 5,000 pound whatever in this room is that with the follow-on product, because you can never know everything, with the follow-on product, there might be some completely novel issue that arises with this new drug, completely different than what you had with the innovator.

If you pose that as the problem, as the critical problem, then, frankly, one could argue that every time you make a manufacturing change, you need to do yet a bigger development program to exclude what you don't know.

Every time you bring on a follow-on, you have to do the same thing.

So what are we looking for here?

DR. SIEGEL: We know, with the history of innovator drugs, that there are completely different and unexpected adverse reactions that emerge from post-marketing surveillance, from post-marketing clinical trials, sometimes related to a change in the product, sometimes just related to more information about the product.

So there is no question that those things are out there. They are out there for innovators, they are out there for generics. They won't go away.

I would agree that registries are best targeted, they can be broad. Sometimes it is to look at what is going to be the effect of chronic use of this drug, something that is hard to look at several years pre-marketing, or through adolescence or pubescence, that tends to be more focused on hormones or growth; sometimes in pregnancy where it is very hard to collect that data.

So it is usually best focused registries, per se, although, as designed, sometimes they pick up unexpected items, and that is, of course, supplemented by post-marketing surveillance, and I would agree with those speakers who said, I think, from both sides, I think, both industries, that said the needs are the same, whether you're an innovator or a follow-on, to do those studies.

DR. WALTON: We have about run out of time. If we have any last comments?

In that case, I will thank you all for coming and participating in the discussion, and look forward to tomorrow's reports.

[Applause.]

[Whereupon, at 5:06 p.m., the session concluded.]

- - -